IN THE UNITED STATES COURT OF FEDERAL CLAIMS
OFFICE OF SPECIAL MASTERS

No. 10-565V
Filed: June 11, 2014
For Publication

MEGAN L. GODFREY,	*	HPV Vaccine; Gardasil; Juvenile Ankylosing Spondylitis; JAS; Causation-in-Fact; Expert; Qualifications.
Petitioner,	*	
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Milton Clay Ragsdale, IV, Ragsdale LLC, Birmingham, AL, for petitioner.
Jennifer Reynaud, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

Vowell, Chief Special Master:

On August 20, 2010, Megan Godfrey ["petitioner"] filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. §300aa-10, *et seq*.[2] [the "Vaccine Act" or "Program"]. The petition alleged that the human papillomavirus ["HPV"] and meningococcal conjugate vaccines Ms. Godfrey received on August 22, 2007, caused her to develop juvenile rheumatoid arthritis. Petition at 1-2.

[1] Because this decision contains a reasoned explanation for my action in this case, it will be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002). As provided by Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the entire decision will be available to the public.

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2006).

To prevail under the Vaccine Act, a petitioner must prove either a "Table" injury[3] or that a vaccine listed on the Table was the cause in fact of an injury (an "off-Table" injury). While both the HPV and meningococcal conjugate vaccines are listed on the Vaccine Injury Table, there are no Table injuries associated with either vaccine.[4]

Although the evidence established that petitioner received the vaccinations alleged, she has failed to demonstrate that either vaccine can or did cause her condition. After considering the record as a whole, I hold that petitioner is not entitled to compensation. *See* § 11(c)(1)(C)(ii)(I).

I. Procedural History.

Ms. Godfrey's petition was accompanied by medical records establishing her receipt of the HPV and meningococcal vaccines on August 22, 2007, her presentation to her family doctor with three months of intermittent hip pain on December 19, 2007, and her diagnosis of juvenile ankylosing spondylitis ["JAS"].[5]

On July 25, 2011, petitioner filed the expert report of Dr. David Axelrod (Petitioner's Exhibit ["Pet. Ex."] 16). Respondent filed the expert reports of Drs. Carlos Rose (Respondent's Exhibit ["Res. Ex."] A) and Burton Zweiman (Res. Ex. C) on September 26, 2011, and October 26, 2011, respectively. Also on October 26, 2011, respondent filed her Rule 4(c) report, recommending against entitlement.

During the Vaccine Rule 5[6] status conference, held on November 16, 2011, I pointed out several problems with petitioner's expert report. I afforded petitioner the opportunity to file a supplemental expert report from Dr. Axelrod or a different expert. Order, issued Nov. 17, 2011, at 1. On April 19, 2012, after filing her remaining medical records, petitioner submitted the expert report of Dr. (Ph.D.) Michael McCabe (Pet. Ex. 52). In response to Dr. McCabe's report, respondent filed Dr. Zweiman's second expert report (Res. Ex. E) on June 18, 2012.

An entitlement hearing was originally scheduled for October 17, 2012. Order, issued July 9, 2012. Due to a subsequent scheduling conflict with respondent's expert,

[3] A "Table" injury is an injury listed in the Vaccine Injury Table (42 C.F.R. § 100.3 (2011)), corresponding to the vaccine received within the time frame specified.

[4] See 42 C.F.R. § 100.3(a)(XV) and (XVI).

[5] This is a condition different from the juvenile rheumatoid arthritis alleged in the petition, but the parties later stipulated that JAS is the correct diagnosis. *See* Joint Prehearing Submissions, filed Nov. 19, 2012, at ¶ 3; *see also infra* at Section IV.C.1 and n. 24.

[6] *See* Rules for Court of Federal Claims, Appendix B, Vaccine Rules.

the hearing was moved to December 10, 2012. Order, issued Aug. 15, 2012. Prior to the hearing, the parties stipulated to the pertinent facts and concluded that the issue to be resolved was whether the HPV vaccine petitioner received on August 22, 2007, "substantially contributed to the development of petitioner's JAS approximately four weeks later."[7] Joint Prehearing Submission, filed Nov. 19, 2012, at 1-2.

On November 28, 2012, petitioners moved to postpone the hearing until her counsel could seek an expert report from her new treating rheumatologist, Dr. Anthony Turkiewicz. Motion, filed Nov. 28, 2012. I denied petitioner's motion, but granted her request to file testimony from Dr. Turkiewicz in the form of an affidavit. Orders, issued Nov. 30, 2012 and Dec. 5, 2012.

Although the petition had identified two vaccines as causal, the evidence presented focused solely on the HPV vaccine. During the hearing, Dr. McCabe testified on behalf of petitioner, and Drs. Rose and Zweiman testified on behalf of respondent. Doctor Axelrod did not testify. On January 18, 2013, petitioner filed a status report that indicated she would not be filing an affidavit from Dr. Turkiewicz.

The parties filed post-hearing briefs on April 1, 2013. Each party filed responsive post-hearing briefs on May 15, 2013, making this case ripe for resolution.

I conclude that petitioner has failed to establish vaccine causation of her condition and thus is not entitled to compensation. The reasons for my conclusion are set forth in more detail below, but in summary, I found the opinions of Drs. Rose and Zweiman more reliable and supported by other evidence than those advanced by Dr. McCabe.[8]

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[7] I will interpret this "substantially contributed" language as the equivalent of the "substantial factor" requirement set forth in *Shyface v. Sec'y, HHS*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). However, I note that since the Federal Circuit's decision in *Shyface*, the Restatement (Third) of Torts has eliminated "substantial factor" in the factual cause analysis. § 26 cmt. j (2010). Because the Federal Circuit has held that the causation analysis in the Restatement (Second) of Torts applies to off-Table Vaccine Act cases (*see Walther v. Sec'y, HHS*, 485 F.3d 1146, 1151 (Fed. Cir. 2007); *Shyface*, 165 F.3d at 1352), this change does not affect the determination of legal cause in Vaccine Act cases: whether the vaccination is a "substantial factor" is still a consideration in determining whether it is the legal cause of an injury.

[8] Petitioner appears to have abandoned the expert opinion of Dr. David Axelrod, a clinical immunologist, filed on July 25, 2011, as Pet. Ex. 16. He had opined that Ms. Godfrey's symptoms "are consistent with the diagnosis of an immune based spondyloarthropathy." Pet. Ex. 16 at 2. His theory was predicated on the assumption that the L1 proteins contained in Gardasil were the same as the L1 proteins found in the body's synovial tissues. His opinion that the vaccine proteins reacted with the receptor binding sites of immune cells resulting in an unwanted immune response against the body was, in essence, based on molecular mimicry. *Id*. This opinion was rebutted by the report of Dr. Rose, who asserted that "there is no biological or chemical relationship between L1 elements [in the vaccine] and the human L1 protein," thus challenging the factual basis for Dr. Axelrod's opinion. Res. Ex. A at 11. Doctor Axelrod did not testify at the hearing in this case, nor did petitioner address Dr. Axelrod's theory in her briefs. Thus, Dr. Axelrod's theory is not addressed in the remainder of this decision. *See* Vaccine Rule (8) regarding waiver.

II. Legal Standards Applying to Off-Table Causation Claims.

When a petitioner alleges an off-Table injury, eligibility for compensation is established when, by a preponderance of the evidence, petitioner demonstrates that she received, in the United States, a vaccine set forth on the Vaccine Injury Table and sustained an illness, disability, injury, or condition caused by the vaccine or experienced a significant aggravation of a preexisting condition. She must also demonstrate that the condition has persisted for more than six months.[9] Vaccine litigation rarely concerns whether the vaccine appears on the Table, the situs for administration, or whether the symptoms have persisted for the requisite time. In most Vaccine Act litigation, the issue to be resolved by the special master is whether the injury alleged was caused by the vaccine.

To establish legal causation in an off-Table case, Vaccine Act petitioners must establish by preponderant evidence: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a proximate temporal relationship between vaccination and injury. *Althen v. Sec'y, HHS,* 418 F.3d 1274, 1278 (Fed. Cir. 2005); *see de Bazan v. Sec'y, HHS*, 539 F.3d 1347, 1351-52 (Fed. Cir. 2008); *Caves v. Sec'y, HHS,* 100 Fed. Cl. 119, 132 (2011), *aff'd per curiam*, 463 Fed. Appx. 932, 2012 WL 858402 (Fed. Cir. 2012) (specifying that each *Althen* factor must be established by preponderant evidence); *Lalonde v. Sec'y, HHS*, 746 F.3d 1334, 1337-38 (Fed. Cir. 2014). The applicable level of proof is the "traditional tort standard of 'preponderant evidence.'" *Moberly v. Sec'y, HHS*, 592 F.3d 1315, 1322 (Fed. Cir. 2010) (citing *de Bazan*, 539 F.3d at 1351; *Pafford v. Sec'y, HHS*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Capizzano v. Sec'y, HHS*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *Althen,* 418 F.3d at 1278)). The preponderance standard "requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence." *In re Winship*, 397 U.S. 358, 371 (1970) (Harlan, J., concurring) (internal quotation and citation omitted).

Another formulation of the causation requirement in off-Table cases is the "Can it cause?" and "Did it cause?" inquiries used in toxic tort litigation. These queries are also referred to as issues of general and specific causation. Prong 1 of *Althen* has been characterized as an alternative formulation of the "Can it cause?" or general causation query. Prong 2 of *Althen*, the requirement for a logical sequence of cause and effect between the vaccine and the injury, has been characterized as addressing the "Did it cause?" or specific causation query. *See Pafford v. Sec'y, HHS*, No. 01-165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff'd*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352. The third *Althen* factor is subsumed into the other inquiries. Even if a particular vaccine has been causally associated with an injury, petitioner must still

[9] Section 13(a)(1)(A). This section provides that petitioner must demonstrate "by a preponderance of the evidence the matters required in the petition by section 300aa–11(c)(1) . . . ." Section 11(c)(1) contains the factors listed above, along with others not relevant to this case.

establish facts and circumstances that make it more likely than not that this vaccine caused his particular injury. Timing may be one of those circumstances.

Whether a case is analyzed under *Althen* or the "Can it cause?" formulation, petitioners are not required to establish identification and proof of specific biological mechanisms, as "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280. The petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the injury or condition; showing that the vaccination was a "substantial factor" in causing the condition and was a "but for" cause are sufficient for recovery. *Shyface*, 165 F.3d at 1352; *see also Pafford,* 451 F.3d at 1355 (petitioner must establish that a vaccination was a substantial factor and that harm would not have occurred in the absence of vaccination). Petitioners cannot be required to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." *Capizzano*, 440 F.3d at 1325. Causation is determined on a case by case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y, HHS,* 35 F.3d 543, 548 (Fed. Cir. 1994). Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280; *but see Knudsen*, 35 F.3d at 550 (when evidence is in equipoise, the party with the burden of proof fails to meet that burden).

By specifying petitioners' burden of proof in off-Table cases as a preponderance of the evidence, directing special masters to consider the evidence as a whole, and stating that special masters are not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record (§13(b)(1)), Congress contemplated that special masters would weigh and evaluate opposing expert opinions in determining whether petitioners have met their burden of proof.[10]

It is now clearly established that special masters may use the framework established by *Daubert v. Merrell Dow Pharmaceuticals*,[11] to evaluate expert testimony on causation. *Andreu v. Sec'y, HHS,* 569 F.3d 1367, 1379 (Fed. Cir. 2009) and *Moberly,* 592 F.3d at 1324; *Terran*, 195 F.3d at 1316 (concluding it was reasonable for the special master to use *Daubert* to evaluate the reliability of an expert's testimony); *Cedillo v. Sec'y, HHS,* 617 F.3d 1328, 1339 (Fed. Cir. 2010) (noting that special masters are to consider all relevant and reliable evidence filed in a case and may use *Daubert* factors in their evaluation of expert testimony); *Davis v. Sec'y, HHS*, 94 Fed. Cl.

[10] *See* § 13(a)(1)(A) (preponderance standard); § 13(a)(1) ("Compensation shall be awarded . . . if the special master or court finds on the record as a whole . . . ."); § 13(b)(1) (indicating that the court or special master shall consider the entire record in determining if petitioner is entitled to compensation and special master is not bound by any particular piece of evidence).

[11] 509 U.S. 579 (1993).

53, 67 (2010) (describing the *Daubert* factors as an "acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted . . . by special masters in vaccine cases"); *see also Snyder v. Sec'y, HHS*, 88 Fed. Cl. 706, 718 (2009) quoting *Ryman v. Sec'y, HHS*, 65 Fed. Cl. 35, 40-41 (2005) (special masters perform gatekeeping function when determining "whether a particular petitioner's expert medical testimony supporting biological probability may be admitted or credited or otherwise relied upon" and as a "trier-of-fact [a special master] may properly consider the credibility and applicability of medical theories").

In summary, special masters decide questions of credibility, plausibility, probability, and reliability, and ultimately determine to which side the balance of the evidence is tipped. *See Pafford*, 451 F.3d at 1359. Bearing all these legal standards in mind, I turn to the evidence presented in this case.

III. Relevant Medical History.

The facts of Ms. Godfrey's medical history are not in dispute. *See* Joint Prehearing Submission at 1-2. She was born on August 1, 1989. Pet. Ex. 8, p. 6. Except for routine childhood illnesses, she was healthy from her birth to the age of 18, when the condition at issue developed. *Id.*; *see also* Pet. Ex. 50. During high school, she participated in athletics, including her high school cheerleading team.[12] *See* Pet. Ex. 50. Her family history is significant for Crohn's disease (father) and rheumatoid arthritis (paternal grandparents and paternal aunts and uncles). Pet. Exs. 7, p. 182; 8, p. 9.

On August 22, 2007, shortly after her eighteenth birthday, Ms. Godfrey received the HPV ["Gardasil"] and meningococcal conjugate vaccines from her pediatrician, Dr. Robinson. Pet. Ex. 2, p. 1.

On December 19, 2007, Ms. Godfrey reported to Dr. Mark Woods, complaining of sharp, intermittent left hip pain for the past three months. Pet. Ex. 3, p. 1. Ms. Godfrey did not recall any injury. *Id*. An X-ray of her left hip was negative. *Id.*, p. 2. Doctor Woods's impression was arthralgia of the hip.[13] Pet. Ex. 3, p. 2. He referred Ms. Godfrey for an MRI[14] to rule out osteomyelitis and to Dr. Steve Lovelady, at DCH Regional Medical Center ["DCH"]. Pet. Exs. 8, p. 86; 11, p. 12.

[12] Ms. Godfrey graduated from high school in May 2007. Petitioner's Post-Hearing Brief ["Pet. Post-Hearing Br."], filed Apr. 1, 2013, at 2 n.2.

[13] He also diagnosed her with microcytic anemia, but this diagnosis does not appear directly relevant to the issues in this case. Pet. Ex. 3, p. 2. Although Dr. McCabe called it "somewhat consistent with an inflammatory response," he also acknowledged that anemia is usually "tied to deficiencies in iron." Transcript from Dec. 10, 2012 Hearing ["Tr."] at 74-75. None of her treating physicians commented on its relevance to her JAS diagnosis.

[14] MRI, or magnetic resonance imaging, is "a method of visualizing soft tissues of the body." DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (32nd ed. 2012) ["DORLAND'S"], at 916.

The MRI, performed on December 28, 2007, showed "[b]ilateral femoral benign fibrous dysplasia," greater on the left side than the right, and left-sided sacroiliitis, which the radiologist thought might have been inflammatory. The radiologist also noted that osteomyelitis is presumed with this appearance. Pet. Ex. 8, p. 86.

Also on December 28, 2007, Ms. Godfrey was seen by Dr. Lovelady, who noted that Ms. Godfrey's father suffered from inflammatory bowel disease and anemia. Pet. Ex. 11, pp. 12-14. On physical examination, Dr. Lovelady found tenderness at the left sacroiliac joint, and decided to admit Ms. Godfrey to DCH for further evaluation to rule out osteomyelitis. *Id*.

Ms. Godfrey saw orthopedist William Standeffer on December 29, 2007. Pet. Ex. 8, pp. 14, 16; *see also* Pet. Ex. 11, p. 12. Based on Ms. Godfrey's MRI, he believed she had "sacroiliitis," which he thought was "probably inflammatory." Pet. Ex. 8, p. 14. He doubted that she had osteomyelitis and noted "fibrous dysplasia [in] both hips." *Id*. Ms. Godfrey was discharged from DCH on December 30, 2007. *Id.*, p. 2. Her relevant discharge diagnoses were the same as her admission diagnoses: hip pain and questionable osteomyelitis. *Id*.

A bone scan on January 8, 2008, showed "increased activity at the left [sacroiliac] joint," indicative of hyperemia and active bone turnover, which "could be seen in osteomyelitis or in an inflammatory sacroiliitis." Pet. Ex. 11, p. 11. An antinuclear antibody screen ["ANA"], a test for autoimmune disease, performed on January 14, 2008, was negative. *Id.*, p. 29. However, an HLA-B27 test, a genetic marker showing susceptibility to conditions such as ankylosing spondylitis, was positive. *Id.*, p. 27.

A steroid injection performed in January 2008 at Children's Hospital of Alabama by Dr. John Doyle relieved Ms. Godfrey's left hip symptoms. Pet. Ex. 9, pp. 89-90. On March 11, 2008, however, she returned to Dr. Doyle complaining of hip pain in the right sacroiliac joint. *Id.*, p. 122. Doctor Doyle's impression was right-sided sacroiliitis. *Id*.

On April 15, 2008, Ms. Godfrey was seen by rheumatologist Randy Cron. Pet. Ex. 7, p. 180. Doctor Cron noted Ms. Godfrey's family history of Crohn's disease and arthritis, and her own history of hip pain. *Id.*, pp. 181-82. Under "[o]ther pertinent past medical history," he wrote, "Gardasil 1st dose in summer prior to all this." *Id.*, p. 182. Doctor Cron also noted Ms. Godfrey's positive HLA-B27 and negative ANA test results, as well as her normal sedimentation rates. *Id.*, p. 181. His diagnosis was HLA-B27 positive spondyloarthropathy. *Id.*, p. 183.

After her initial visit with Dr. Cron in April 2008, Ms. Godfrey continued to receive treatment, including Infliximab[15] injections for her spondyloarthropathy. Pet. Exs. 7, pp. 73-77, 94-98, 132-35, 149-52, 157-61; 9, pp. 12-13.

On August 22, 2012, Ms. Godfrey had an initial visit with rheumatologist Anthony Turkiewicz. Pet. Ex. 88, pp. 10-14. She was seen for a follow up visit on September 17, 2012. *Id.*, pp. 7-9. Doctor Turkiewicz's impression was anklylosing spondylitis/axial spondyloarthropathy. *Id.*, p. 9. He continued Ms. Godfrey's Infliximab injection treatments. *See id.*, pp. 3, 7, 10-11, 40. According to Ms. Godfrey, "[t]his treatment has been successful in terminating [her] symptoms." Pet. Post-Hearing Br. at 2.

IV. Medical Opinions and Other Evidence.

Ms. Godfrey's JAS diagnosis is clear and uncontested. Equally clear is that the clinical symptoms of her condition first manifested around September 19, 2007, about four weeks after her August 22, 2007 receipt of her only Gardasil vaccine and three months before she first sought medical treatment for those symptoms. *See* Pet. Exs. 2; 3, p. 1. The sole contested matter in this case is whether Ms. Godfrey's HPV vaccination "substantially contributed" to the development of her JAS. Joint Prehearing Submission at 2. Ms. Godfrey contends that the Gardasil vaccine elicited an immune response, specifically "a pro-inflammatory cytokine milieu," that substantially contributed to the development of her condition. Pet. Post-Hearing Br. at 6-7. Respondent maintains, however, that Ms. Godfrey's JAS "emerged by chance, in the context of a strong genetic predisposition." Respondent's Post-Hearing Brief ["Res. Post-Hearing Br."], filed Apr. 1, 2013, at 2.

Expert qualifications play a significant role in the weight given to expert opinions, particularly when the opinions expressed are otherwise inadequately supported by reliable evidence. *See Moberly*, 592 F.3d at 1325 ("Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and we have made clear that the special masters have that responsibility in Vaccine Act cases.") (citations omitted).

In this case, I have accorded the opinions of respondent's experts greater weight, based not only on their qualifications, but also on the lack of support for Dr. McCabe's rather speculative pro-inflammatory cytokine theory in this case. Although pro-inflammatory cytokines may play a role in JAS's symptomatology, there is little evidence that they play a role in JAS's pathogenesis. Likewise, there is little evidence that one dose of Gardasil causes significant or persisting increases in cytokine levels. I thus conclude that there is inadequate evidence that the Gardasil vaccination on August 22, 2007 substantially contributed to the development of Ms. Godfrey's JAS.

[15] Injections of Infliximab, a chimeric monoclonal antibody, inhibits tumor necrosis factor-α (TNF-α) and other pro-inflammatory cytokines. PHYSICIAN'S DESK REFERENCE (58th ed. 2004), at 1145.

I begin the more detailed analysis of the causation evidence with a comparison of the qualifications of the expert witnesses, followed by a discussion of the human papillomaviruses, human papillomavirus vaccines, and JAS, followed by a summary of the expert opinions and the relevant medical literature. I conclude with an analysis of how the evidence stacks up against the *Althen* factors.

A. The Parties' Experts and their Qualifications.

1. Michael McCabe, Ph.D.

Doctor McCabe is trained in microbiology, immunology, and toxicology, but he is not a medical doctor. Pet. Ex. 53 at 2; Tr. at 5, 7, 9. He earned a B.S. in biology from Siena College in 1984, and an M.S. in microbiology and immunology from Albany Medical College in 1990. In 1991, he earned a Ph.D. in microbiology and immunology, also from Albany Medical College. Pet. Ex. 53 at 2. From 1990 to 1992, Dr. McCabe was a postdoctoral research associate at the Karolinska Institute in Stockholm, Sweden. *Id*. Between 1992 and 2000, he held various teaching positions related to chemical toxicology at Wayne State University in Detroit, Michigan. *Id*. During his final three years at Wayne State (1997-2000), Dr. McCabe was the director of a facility engaged in molecular cell biology research projects, including projects related to intracellular cytokine analysis. *Id*.

Since 2000, Dr. McCabe has been a professor at the University of Rochester School of Medicine and Dentistry in Rochester, New York, first as an associate professor and since 2009 as an adjunct associate professor. Pet. Ex. 53 at 1. At the University of Rochester, he has served in three primary capacities—as a researcher, teacher, and administrator. *Id*. As a researcher, he oversaw an NIH-funded program involving "mechanistic metal toxicology and immunotoxicology." *Id*. He lectured on metal toxicity, as well as cell signaling and immunity. In his administrative role, Dr. McCabe served on university committees, including those related to environmental health sciences research and toxicology training. *Id*.

Dr. McCabe's primary employment involves reviewing cases and testifying in commercial and personal injury litigation involving environmental and occupational exposures for Robson Forensic. Pet. Ex. 53 at 1; Tr. at 5-6, 10. Specifically, Dr. McCabe undertakes investigations, produces reports, and offers testimony concerning exposures to various agents, including metals and solvents. Pet. Ex. 53 at 1. About 80% of his professional time and about 95% of his income is derived from his work at Robson Forensic. Tr. at 11. He has reviewed about eight vaccine injury claims while a consultant with Robson Forensic.[16] Tr. at 6.

[16] Prior to beginning work at Robson Forensic in 2009, Dr. McCabe testified for respondent about metal toxicology and immunotoxicology in at least one vaccine injury case. *See Snyder v. Sec'y, HHS*, No. 01-162V, 2009 WL 332044, at *18 (Fed. Cl. Spec. Mstr. Feb. 12, 2009).

Doctor McCabe has authored or co-authored 12 book chapters and about 40 articles published in peer-reviewed publications. Pet. Ex. 53 at 8-13. The focus of his research has been "the role of heavy metals as environmental triggers in producing diseases of the immune system." Tr. at 11-12.

Doctor McCabe testified that his "understanding of cellular immunology, immune mechanisms, [and] immune mediated diseases" is relevant to the causation issue in this case. Tr. at 7; *see also* Tr. at 9. He added that, throughout his 25 year academic career, he has had to "analyze and to understand . . . the triggers for diseases . . . [and] the environmental and genetic risk factors for diseases," as well as how they "interact and lead to particular outcomes." Tr. at 10. Additionally, Dr. McCabe noted that he previously testified in a case before another special master involving juvenile idiopathic arthritis, a condition similar to Ms. Godfrey's, which the petitioner alleged was caused by the Gardasil vaccine. Tr. at 8. In that case, Dr. McCabe also offered opinions regarding cytokine production as a trigger for the onset of the condition.[17] Tr. at 8.

2. Carlos Rose, M.D.

Doctor Rose is a board certified pediatric rheumatologist. Res. Ex. B at 3-6; Tr. at 100. He graduated from the University of Buenos Aires School of Medicine in 1977. Res. Ex. B at 1; Tr. at 100. He did the majority of his post-graduate training in internal medicine in Buenos Aires between 1979 and 1983, and was a fellow in rheumatology at Buenos Aires National Institute of Rehabilitation. Res. Ex. B at 4-5; Tr. at 100. In 1987, he moved to the United States for pediatric training and fellowships in pediatric rheumatology at the Children's Hospital of Philadelphia and the Alfred I. duPont Institute. Res. Ex. B at 5; Tr. at 100.

Since 1991, Dr. Rose has been a staff physician in pediatric rheumatology at the duPont Institute, as well as a professor of pediatrics at Thomas Jefferson University's Jefferson Medical College. Res. Ex. B at 6; Tr. at 100. In 1994, he became the head of the duPont Institute's Division of Rheumatology. Res. Ex. B at 7; Tr. at 100. Doctor Rose spends about 50% of his professional time performing clinical functions, 40% doing "research ethics," and 10% doing actual research. Tr. at 100.

In addition to his clinical and teaching work, Dr. Rose has held, and continues to hold, memberships with boards, societies, and committees related to pediatrics and rheumatology. For over 10 years, he has been a member of the Pediatric Rheumatology Collaborative Study Group and the Pediatric Rheumatology European Society. Res. Ex. B at 9. In 2002, he chaired a pediatric symposium on infection-

[17] In a decision issued after Dr. McCabe's testimony in this case, the special master rejected Dr. McCabe's causation theory. *Koehn v. Sec'y, HHS*, No. 11–355V, 2013 WL 3214877 at *28 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review denied*, 113 Fed. Cl. 757 (2013), *appeal docketed*, No. 14-5054 (Fed. Cir. Feb. 18, 2014).

related arthritis. *Id.* at 10. Between 2006 and 2008, he served as a member of a board monitoring the safety of aggressive therapy to treat juvenile idiopathic arthritis. *Id.* at 8. During the same period, he served on an advisory board on juvenile idiopathic arthritis for Brystol-Myers-Squibb. *Id*. Doctor Rose is also on the editorial board of CLINICAL RHEUMATOLOGY. *Id.* at 9. Additionally, he has authored or co-authored multiple book chapters and over 70 papers published in peer-reviewed publications, including papers on juvenile rheumatoid arthritis and juvenile idiopathic arthritis. *Id.* at 8-20.

Doctor Rose has treated hundreds of children with spondyloarthropathies. Tr. at 100-01. He has testified in other Vaccine Act cases, exclusively for the Department of Health and Human Services. Tr. at 102.

3. Burton Zweiman, M.D.[18]

Doctor Zweiman was board certified in internal medicine, allergy and clinical immunology, and laboratory immunology. He earned his undergraduate and medical degrees from the University of Pennsylvania in 1952 and 1956, respectively. Res. Ex. D at 1-2; Tr. at 174. Between 1956 and 1959, he did his post-graduate work at Mt. Sinai Hospital (New York City), the University of Pennsylvania Hospital, and Bellevue Hospital Center (New York City). Res. Ex. D at 1; Tr. at 174. Thereafter, he held a fellowship in allergy and immunology with the University of Pennsylvania Hospital and NYU Medical Center. Res. Ex. D at 1.

Between 1963 and his death, Dr. Zweiman held various teaching positions at the University of Pennsylvania School of Medicine, becoming a full professor in 1975. Res. Ex. D at 1-2. Between 1969 and 1998, he was the chief of the allergy and immunology division of the University of Pennsylvania Medical Center. Res. Ex. D at 2; Tr. at 173.

In addition to his clinical and teaching duties, Dr. Zweiman held positions with various boards, societies, and committees. Between 1971 and 2001, he was an active member of the American Academy of Allergy and Immunology, serving on the board of directors for over 10 years and as the chairman for a year. Res. Ex. D at 2-3. In 1986 and 1987, he was a member of review panels concerned with arthritis research. *Id.* at 4. Additionally, he held positions on several editorial boards, including that of the Journal of Allergy and Clinical Immunology, where he served as editor between 1988 and 1993. *Id.* at 3. He was published over 200 times on various allergy and immunology topics, including the study of T-cells, lymphocytes, and cytokines. *Id.* at 6-44.

Doctor Zweiman testified on behalf of respondent in hearings six or seven times. Tr. at 174. In this case, he was offered as an expert in immunology. Tr. at 175.

[18] On January 2, 2014, a representative from the Department of Justice contacted the Office of Special Masters to convey the unfortunate news of Dr. Zweiman's death.

B. Human Papillomaviruses and Human Papillomavirus Vaccines.

1. Human Papillomaviruses.

There are over 130 types of human papillomaviruses ["HPVs"]. M. Stanley, *Immunobiology of HPV and HPV vaccines*, GYNECOLOGIC ONCOLOGY, 109: S15-S21 (2008), filed as Pet. Ex. 62 ["Stanley I, Pet. Ex. 62"], at S15. The virus is a small, non-enveloped, double-stranded DNA virus. L. Villa, et al., *Immunologic response following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, and 18*, VACCINE, 24: 5571-83 (2006), filed as Pet. Ex. 31 ["Villa, Pet. Ex. 31"], at 5572. These viruses fall into two groups—low-risk types, such as HPV 6 and 11, which cause benign warts, and high-risk types, such as HPV 16 and 18, which cause cervical cancer. Stanley I, Pet. Ex. 62, at S15-16.

HPVs have the ability to evade the host's immune defenses, largely because they primarily infect epithelial cells. Epithelial cells do not mount a robust immune response to these viruses. *See* I. Frazer, *Correlating immunity with protection for HPV infection*, INTL. J. INFECTIOUS DISEASES, 11: S10-S16 (2007), filed as Pet. Ex. 71 ["Frazer II, Pet. Ex. 71"], at S11 (providing several explanations for the poor immune response to the natural virus infections). In individuals previously unexposed to HPVs, an immune response to the virus involves "little or no release into the local milieu of pro-inflammatory cytokines."[19] Stanley I, Pet. Ex. 62, at S16.

Most genital HPV infections (80% - 90%) resolve over time as HPVs "are cleared as a result of a successful cell-mediated[20] immune response." Stanley I, Pet. Ex. 62, at S17. A minority of individuals (10% - 20%), however, remain infected and are at risk of developing disease. *Id.* One explanation for the persistence of an HPV infection is the host's poor natural antibody response. *Id.* at S17-18.

2. Human Papillomavirus Vaccines.

a. Design and Delivery.

To create a vaccine against HPVs, virologists had to find a way to stimulate the immune system to create neutralizing antibodies, as research had confirmed that HPV neutralizing antibodies were protective against infections. Stanley I, Pet. Ex. 62, at S18. Virologists sought to produce neutralizing antibodies to HPV by creating vaccines with virus-like particles ["VLPs"]. VLPs are "empty, non-infectious viral capsids that

[19] Pro-inflammatory cytokines are "proteins released by one cell population . . . on contact with specific antigen" that are "capable of stimulating inflammation." DORLAND'S at 466 (defining "cytokine"), 1523 (defining "pro-inflammatory").

[20] Cell-mediated immune response refers to the adaptive immune response in which T-cells have the central role. DORLAND'S at 917.

structurally mimic the outer shell of the virion." L. Pinto, et al., *HPV-16 L1 VLP vaccine elicits a broad-spectrum of cytokine responses in whole blood*, VACCINE, 23: 3555-64 (2005), filed as Pet. Ex. 73 ["Pinto I, Pet. Ex. 73"], at 3555. Vaccines containing VLPs induce "high concentrations of neutralizing antibodies" and "activate both innate and adaptive immune responses." Stanley I, Pet. Ex. 62, p. S18. These vaccines are delivered directly into the muscle, "resulting in rapid access to the local lymph nodes, thus circumventing the immune avoidance strategies of the [viruses]." *Id.* at S17. Consequently, HPV vaccines stimulate greater antibody production than the virus does during natural infections. *Id.* at S18; *see also* Tr. at 30-31 (McCabe) ("This is a very potent immunogen in comparison to the natural infection.").[21]

b. Gardasil Vaccine.

Gardasil is one of two approved vaccines against HPV. It contains reproductions of the L1 portion of four types of the virus. The L1 VLPs in Gardasil have been shown to be effective against four viral types, 6, 11, 16, and 18. M. Stanley, *HPV – immune response to infection and vaccination*, INFECTIOUS AGENTS & CANCER, 5: 1-6 (2010), filed as Pet. Ex. 63 ["Stanley II, Pet. Ex. 63"], at 3. It is administered in a three dose series, with the second dose administered two months after the first dose, and the third administered six months after the first dose. B. Slade, et al., *Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine*, JAMA, 32(7): 750-57 (2009), filed as Res. Ex. C-2 ["Slade, Res. Ex. C-2"], at 750.

Gardasil was extensively tested prior to being approved for use in the United States. Doctor Zweiman testified that Gardasil appears to be one of the safest vaccines marketed. Tr. at 184 (discussing comments about the vaccine in the medical and immunological communities). Several of the medical literature exhibits filed by both parties in this case were based on these pre-marketing studies at Johns Hopkins University. *See, e.g.,* Pinto I, Pet. Ex. 73. Studies of Gardasil continued after licensure. *See, e.g.,* C. Chao, et al., *Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine*, J. INTERNAL MED., 271: 193-203 (2012), filed as Pet. Ex. 80 and Res. Ex. C-23 ["Chao, Pet. Ex. 80"], at 194; T.C. Pomfret, et al., *Quadrivalent human papillomavirus (HPV) vaccine: a review of safety, efficacy, and pharmacoeconomics*, J. CLINCAL PHARMACY & THERAPEUTICS, 36: 1-9 (2011), filed as Res. Ex. C-5 ["Pomfret, Res. Ex. C-5"], at 4. As Dr. Zweiman testified (Tr. at 182), over 35 million doses of Gardasil have been administered to more than 20 million individuals since licensure.[22]

[21] Some of the filed medical literature indicates that it is not the "potency" of the vaccine VLPs that stimulates the greater immune response, but rather the mechanism of inducing them. Wild-type HPV viruses invade epithelial cells, which do not generate the same robust immune response to the virus as the tissue into which the vaccine VLPs are injected. Stanley I, Pet. Ex. 62, at S16, S18.

[22] The 35 million figure was based on data as of June 2011. Centers for Disease Control and Prevention, *Vaccine Safety: Reports of Health Concerns Following HPV Vaccination*,

Gardasil and the other HPV VLP vaccine have been shown to produce a response by both the adaptive and innate arms of the immune system. Stanley I, Pet. Ex. 62, at S18.

c. Antibody (Adaptive) Immune Response.

By design, HPV vaccines stimulate greater antibody production than the natural viruses. Stanley I, Pet. Ex. 62, at S18; *see also* Tr. at 30-31 (Dr. McCabe). This quality is "fairly uncommon" among vaccines. Villa, Pet. Ex. 31, at 5581; *see also* Stanley I, Pet. Ex. 62, at S18 ("[T]he peak geometric mean antibody concentrations achieved are at least two logs higher than those after natural seroconversion.").[23] After the three-shot series, antibody concentrations "are 1-4 logs higher than those in natural infections." Stanley II, Pet. Ex. 63, at 4. The peak antibody response occurs about one month after the final dose (the third dose) in the vaccination schedule. *Id.*

An immunogenicity study of Gardasil showed that the antibody response of the vaccinated group, who had received the complete three injection series, was approximately 10 to 100 times greater than the unvaccinated control group, who had prior natural infection. Among the vaccinated group, the immune response began approximately one month after the initial dose, peaked at approximately month seven, and thereafter declined to a plateau for two and a half years after the last dose. Frazer II, Pet. Ex. 71 at S12-13; *see also* Villa, Pet. Ex. 31, at 5578; E. Joura, et al., *HPV antibody levels and clinical efficacy following administration of a prophylactic quadrivalent HPV vaccine*, VACCINE, 26: 6844-51 (2008), filed as Pet. Ex. 68 ["Joura, Pet. Ex. 68"], at 6849; A. García-Piñeres, et al., *Cytokine and Chemokine Profiles following Vaccination with Human Papillomavirus Type 16 L1 Virus-Like Particles*, CLINICAL & VACCINE IMMUNOLOGY, 14(8): 984-89 (2007), filed as Pet. Ex. 74 ["García-Piñeres, Pet. Ex. 74"], at 986.

d. Cytokine Immune Response.

In addition to inducing greater antibody production than natural infection, HPV vaccines have been shown to induce "cell mediated immune responses, including T cell proliferative . . . and cytokine responses." Pinto I, Pet. Ex. 73, at 3555. Because the role of T-cells in mediating antibody production is poorly understood, researchers have

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http://www.cdc.gov/vaccinesafety/Vaccines/HPV (printed Sept. 5, 2011), filed as Res. Ex. C-6 ["CDC, Res. Ex. C-6"], at 1.

[23] There was no evidence, however, that the immune response to Gardasil is different than the immune response to other vaccines, simply that it is stronger than the body's response to natural infection. Doctor McCabe indicated that other vaccines would cause a similar qualitative pro-inflammatory cytokine response (Tr. at 58), but he could not say whether the response would be quantitatively similar (*id.*). In other words, according to Dr. McCabe, vaccines in general provoke the same types of cytokine responses, but he was unaware whether they provoked the same increases or decreases in cytokine levels.

focused on measuring cytokine responses as a surrogate for T-cell responses. Researchers have theorized that "[c]ytokine profiling, as a measure of T cell responses, may offer insights into mechanisms of protection against disease and help explain the consistently strong antibody responses induced by the [HPV] vaccine." *Id.*

C. Juvenile Ankylosing Spondylitis.

1. Ms. Godfrey's Diagnosis.

Despite some discrepancies in the record regarding Ms. Godfrey's diagnosis[24] prior to the hearing, the parties ultimately agreed that Ms. Godfrey suffered from juvenile ankylosing spondylitis ["JAS"]. Joint Pre-Hearing Submission at ¶ 3. *See* Pet. Ex. 52 (Expert report of Dr. McCabe) at 3; Res. Ex. A (Expert report of Dr. Rose) at 2. I conclude that JAS is the correct diagnosis.

JAS is the pediatric form of ankylosing spondylitis ["AS"]. Res. Ex. A (Rose) at 2. The "juvenile" modifier is applied to those under 16 years of age who exhibit the symptoms of AS. Pet. Ex. 52 (McCabe) at 3;[25] Y. Lin, et al., *Differences Between Juvenile-onset Ankylosing Spondylitis and Adult-onset Ankylosing Spondylitis*, J. CHIN. MED. ASSOC., 72(11): 573-80 (2009), filed as Pet. Ex. 56 ["Lin, Pet. Ex. 56"], at 573. Although the experts acknowledged that Ms. Godfrey was over 16 at the time of her diagnosis, they were satisfied with the JAS diagnosis. Pet. Ex. 52 (Dr. McCabe) at 3 ("[A]ccordingly her diagnosis with JAS was consistent with her having an early onset with the adult form of the disease."); Res. Ex. A (Dr. Rose) at 2 (expressing his comfort using the acronym JAS to describe Ms. Godfrey's condition). Although there are some differences in symptomology between JAS and AS, they are, in essence, the same disease.

2. Symptomology.

The primary differences in clinical manifestation between AS and the juvenile form, JAS, is the location of the enthesitis[26] or arthritis. Where the initial symptoms of

[24] Rheumatologist Randy Cron used the term "spondyloarthropathy" Pet. Ex. 7, p. 183. Rheumatologist Anthony Turkiewicz diagnosed Ms. Godfrey with "ankylosing spondylitis/axial spondyloarthropathy." Pet. Ex. 88, p. 9. In her petition, however, Ms. Godfrey alleged that she suffered from "juvenile rheumatoid arthritis." Petition at 1. Ms. Godfrey's first expert, Dr. Axelrod, classified her condition as "immune based spondyloarthropathy" (Pet. Ex. 16 at 2) and "immune arthropathy (Juvenile spondyloarithitis)." Pet. Ex. 16 at 3. Later, in her pre-hearing brief, Ms. Godfrey stated that she and her expert would refer to her condition as "juvenile idiopathic arthritis." Pet. Pre-Hearing Br. at 5. Finally, in her post-hearing brief, she identifies her diagnosis as "juvenile ankylosing spondylitis." Pet. Post-Hearing Br. at 6.

[25] Doctor McCabe's expert report includes two sets of page numbers. This decision will refer to his report using the computerized Bates stamped numbers.

[26] Enthesitis is "inflammation of the muscular or tendinous attachment to bone." DORLAND'S at 627; *see also* M. Dougados and D. Baeten, *Spondyloarthritis*, LANCET, 377: 2127-37 (2011), filed as Pet. Ex. 54

AS are mainly axial, the onset of JAS typically includes peripheral arthritis and peripheral enthesopathies. Lin, Pet. Ex. 56, at 573-74, 578-79; H. Chen, et al., *Clinical, Functional, and Radiographic Differences Among Juvenile-onset, Adult-onset, and Late-onset Ankylosing Spondylitis*, J. RHEUMATOL., 39(5): 1-6 (2012), filed as Pet. Ex. 57 ["Chen, Pet. Ex. 57"], at 2, 4. The areas commonly affected in JAS are the pelvis, heels, knee joints, and hip joints. Lin, Pet. Ex. 56, at 575. In JAS, versus AS, there is "a tendency for more radiographic hip disease" (Chen, Pet. Ex. 57, at 4), affecting the sacroiliac joints (S. Tse and R. Laxer, *New advances in juvenile spondyloarthritis*, NAT. REV. RHEUMATOL., 8: 1-11 (2012), filed as Pet. Ex. 55 ["Tse, Pet. Ex. 55"], at 1).[27] This is precisely the pattern Ms. Godfrey displays.

The severity of the disease is scored, based on the "irreversible structural damage caused by the disease, often due to tissue remodeling and its functional consequences." Dougados, Pet. Ex. 54, at 2132.

3. Risk Factors.

There are several risk factors for JAS. Researchers have estimated that "genetic risk factors contribute to 80-90% of the susceptibility to [AS]." Dougados, Pet. Ex. 54 at 2128; *see also* Lin, Pet. Ex. 56, at 578. The primary genetic risk factor is HLA-B27, which has been described as a "direct and dominant effect." Dougados, Pet. Ex. 54, at 2129; *see also* Lin, Pet. Ex. 56, at 579. HLA-B27 is present in 80-90% of patients with AS. Dougados, Pet. Ex 54, at 2129. In patients with JAS, it is even more prevalent. In a study of 47 patients with JAS, over 97% were positive for HLA-B27. Lin, Pet. Ex. 56, at 577.[28] A negative result, however, "does not preclude the presence of spondyloarthritis." Dougados, Pet. Ex. 54, at 2128. Moreover, "only a small proportion of people in the general population who harbour HLA-B27 (5-6% in white people) develop [AS], and HLA-B27 explains only 20-40% of the genetic susceptibility to [AS]—suggesting the contribution of additional genes." *Id.* at 2129.

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and Res. Ex. C-1 ["Dougados, Pet. Ex. 54"], at 2128 (defining "enthesopathy" as "inflammation at the bone insertion sites of ligaments and tendons").

[27] With the exception of some onset features, specifically the prevalence of peripheral arthritis and peripheral enthesopathies, JAS resembles AS "in [its] association with HLA-B27 and bacteria, clinical expression, and radiological features." Additionally, it appears that both JAS and AS "share common pathogenetic mechanisms." R. Burgos-Vargas, *Juvenile onset spondyloarthropathies: therapeutic aspects*, ANN. RHEM. DIS., 61(Suppl. III): iii33-iii39 (2002), filed as Pet. Ex. 61 ["Burgos-Vargas, Pet. Ex. 61"], at iii33. Consequently, references to AS also likely apply to JAS.

[28] *See also* NELSON TEXTBOOK OF PEDIATRICS (19th ed. 2011) ["NELSON'S "], at Pt. XV, Ch. 150, Lab. Findings, https://expertconsult.inkling.com/read/nelson-pediatrics-kliegman-behrman-19th/chapter-150/chapter150-reader-4 (noting that "HLA-B27 is present in > 90% of children with JAS.").

In addition to genetic factors, specific types of infection (gastrointestinal or genitourinary infection), and physical trauma are also risk factors for JAS. Lin, Pet. Ex. 56, at 578; Tr. at 195-97 (Dr. Zweiman). JAS is closely linked to gut inflammation, in association with Crohn's disease. Burgos-Vargas, Pet. Ex. 61, at iii34. The incidence of non-specific inflammatory bowel disease in patients with JAS is about 80%. *Id.* at iii35. Intense physical training has been observed in JAS patients before symptom onset. Lin, Pet. Ex. 56, at 578.

4. Treatment.

Treatments for JAS are "aimed at alleviating symptoms of inflammation (that is, pain), maintaining or improving range of motion and muscle strength, preventing deformity, preserving function, and preventing or managing disease complications." Burgos-Vargas, Pet. Ex. 61, at iii36; *see also* Dougados, Pet. Ex. 54, at 2132. In addition to physical and occupational therapy, non-steroidal anti-inflammatory drugs ["NSAIDs"] are used to treat JAS. Burgos-Vargas, Pet. Ex. 61, at iii36; Dougados, Pet. Ex. 54, at 2132 (identifying NSAIDs as "the cornerstone pharmacological intervention" for AS).

Agents that target tumor necrosis factor alpha ["TNF-α"], including etanercept and Infliximab, are also used to treat JAS. Burgos-Vargas, Pet. Ex. 61, at iii37. TNF-α is a pro-inflammatory cytokine "that mediates several inflammatory and immunoregulatory activities." *Id.* High levels of TNF-α have been documented in the synovial tissue of patients with JAS. *Id.* at iii37. "Increased production of TNF-α correlates closely with increased infiltration of inflammatory cells (T cells and macrophages) into the synovia." *Id.* at iii34. However, despite the success of anti-inflammatory drugs in providing symptomatic relief, current JAS treatments, including drugs like Infliximab, "do not alter the natural course of the disease." *Id.* at iii37.

D. Petitioner's Evidence.

Doctor McCabe opined that Ms. Godfrey's Gardasil vaccination triggered, thus substantially contributing to, the manifestation of her JAS. Tr. at 16. His theory, which he described as a "biologically plausible" mechanism, was that the vaccination triggered the release of proinflammatory cytokines, causing her JAS. Tr. at 16; Pet. Ex. 52 at 7.

Doctor McCabe explained that JAS is a disease with an autoinflammatory etiology.[29] The disease process is "driven by dysregulation of the innate immune

[29] Autoinflammatory diseases should not be confused with autoimmune diseases. "Autoimmune diseases are characterized by unchecked T-cell and/or B-cell reactivity to self-antigens, leading to chronic tissue inflammation." C. Ambarus, et al., *Pathogenesis of spondyloarthritis: autoimmune or autoinflammatory?*, CURR. OPIN. RHEUMATOL., 24: 1-8 (2012), filed as Pet. Ex. 79 ["Ambarus, Pet. Ex. 79"], at 1. In contrast, autoinflammatory diseases do not involve attacks by the immune system on host tissues; they involve "innate immune responses to specific tissue triggers, such as microorganisms or microtrauma." *Id.*

system." Pet. Ex. 52 (Dr. McCabe) at 3. The causes of JAS are "multifactorial," with "genetic susceptibility factors and environmental triggers working together in complex ways to initiate and perpetuate adaptive and innate immune activities resulting in tissue damage." *Id.* Doctor McCabe acknowledged Ms. Godfrey's genetic susceptibility, noting the "high association between HLA-B27 and spondyloarthritis." *Id.*; *see also* Tr. at 20, 23, 48-49. He also noted her father's Crohn's disease and its "link" to cytokine expression as a genetic risk factor.[30] Tr. at 21.

Doctor McCabe testified that bacterial or mechanical stressors have been implicated in the etiology of spondyloarthropathies (Tr. at 22, 26), but the evidence that "infection, stress, and trauma are all triggers associated with the onset of JAS" is "[l]argely temporal" (Tr. at 85). He noted that "a large number of people" with JAS "have had a traumatic event or a bacterial infection." Tr. at 22, 26, 85; *see also* Dougados, Pet. Ex. 54, at 2129-30. Doctor McCabe acknowledged the absence of studies identifying an association between vaccines and spondyloarthropathies, but added that there is some overlap in the stimulation of pro-inflammatory cytokines between bacterial infections and vaccines and bacterial infections are known triggers for spondyloarthropathies. Tr. at 26-27, 34-35.

The Gardasil vaccine is designed to elicit an immune response greater than that induced by natural HPV infection. Pet. Ex. 52 (Dr. McCabe) at 4. This immune response is characterized by high anti-HPV L1 VLP antibody titers, as well as "high levels of both adaptive and innate immune cytokines." *Id.* (citing Pinto I, Pet. Ex. 73) [31] Doctor McCabe stated that the L1 viral capsid protein in Gardasil "induce[s] high titers of neutralizing antibodies to the L1 [protein]." Pet. Ex. 52 at 4. He added that "the peak geometric mean antibody levels that are achieved are reported to be 100-fold higher than those that occur due to natural seroconversion as a consequence of HPV infection." *Id.* According to Dr. McCabe, "[t]his strong antibody response is expected to be, and is, controlled by the activities of T cells including production of T cell derived cytokines." *Id.* at 5. He added that many of the adaptive and innate cytokines elicited by the Gardasil vaccine are the "pro-inflammatory cytokines that have been implicated in the etiology[32] of auto-inflammatory disorders like [JAS]." Pet. Ex. 52 at 4. Included among these pro-inflammatory cytokines are TNF-α and interleukins ["IL"] 1, 6, 17, and 23. *Id.* at 5. Doctor McCabe stated that the natural HPV infection "produces little or no pro-inflammatory cytokine release, and if anything stimulates an anti-inflammatory cytokine cascade." Tr. at 34.

[30] Doctor Zweiman appeared to disagree that Crohn's disease was causally linked to cytokines such as TNF-α. *See* Tr. at 181.

[31] This quotation somewhat misstates both the study's focus and results, which are discussed in more detail *infra* at Section V.A.1.

[32] Doctor McCabe's phraseology of "implicated in the etiology" suggests that pro-inflammatory cytokines are causal or pathogenic. This was countered by Dr. Rose's testimony. Tr. at 116-18.

During the hearing, Dr. McCabe was asked for the best evidence that the Gardasil vaccine is an environmental factor linked to AS. Tr. at 50. He responded that, in "producing a common element of the disease"—innate immune system activation—the vaccine "serves as a trigger in [a] genetically predisposed individual." *Id.* He added that the "vaccine is doing exactly what it's intended to do" in stimulating an innate immune system response. *Id*.

Later, it became unclear whether Dr. McCabe was contending that Ms. Godfrey's genetic predisposition rendered her more susceptible to a normal cytokine-driven immune activation, or that the vaccine caused an abnormally high level of cytokine production in Ms. Godfrey. Tr. at 50-51, 54-56. His characterization of the role of cytokine production in response to HPV vaccination was inconsistent. During his cross-examination, he agreed with respondent's summation of his theory that "the abnormal production of certain cytokines plays . . . a significant role in the etiology of ankylosing spondylitis." Tr. at 45. Shortly thereafter, however, he stated, "I'm not saying that [the vaccine is] triggering an abnormal production of those cytokines," rather it causes the production of pro-inflammatory cytokines "[t]hat are serving as a trigger for disease in a susceptible individual." Tr. at 50-51; *see also* Tr. at 54.[33]

However, Dr. McCabe was consistent in his assertion that Gardasil stimulated cytokine production in Ms. Godfrey, specifically the production of TNF-α, and that this immune response, when combined with her genetic susceptibility, caused Ms. Godfrey to develop JAS. Tr. at 45-47; *see also* Tr. at 16, 28-29. By way of analogy, he testified that a genetically susceptible person such as Ms. Godfrey is climbing a hill towards development of the disease throughout her life, but the Gardasil vaccine hastened her assent, pushing her to the peak. Tr. at 56.

He also stated that, for JAS to manifest, there must be "sustained elevation of the cytokines and the abnormality in the regulation of the cytokine[s] in order for the disease to manifest and to continue to manifest." Tr. at 57. He testified that "the basis of why people who have this disease and diseases like it are on anti-TNF drugs for a long period of time, is that there is a sustained disregulation in the production of cytokines." *Id*. He did not point to any evidence that Gardasil caused a sustained elevation in cytokines in recipients. Tr. at 75-77.

[33] Doctor McCabe later clarified that the cytokine response to vaccination is not abnormal, rather it is "the abnormality in the regulation of the cytokine" that causes the disease to manifest and continue to manifest. Tr. at 57. Even later, however, Dr. McCabe failed to correct respondent when she asked, "What is your best evidence that Megan had an abnormally high level of any of the cytokines that you mentioned." Tr. at 73-74.

With regard to timing, Dr. McCabe opined that "the expected interval between vaccination and the onset of the autoinflammatory trigger is predicted by the time period that measurable changes in the immune response are known to be elicited by the vaccine." Pet. Ex. 52 at 5; *see also* Tr. at 75-76. He referenced studies showing that nearly all individuals who received three doses of Gardasil at zero, two, and six months seroconverted[34] within seven months. Pet. Ex. 52 at 5-6. When he was asked why four weeks would be an appropriate medical time frame for the development of JAS, Dr. McCabe stated that four weeks and earlier is "the time that the immune response is elicited by the vaccine." Tr. at 79. He also testified that, considering Ms. Godfrey only received one dose of Gardasil, he would be "less inclined to think that the vaccine or the cytokines elicited by the vaccine . . . was the trigger" had she not presented with symptoms within two months of vaccination. Tr. at 78; *see also* Tr. at 38, 84.

Doctor McCabe testified that the best evidence that a single dose of the HPV vaccine can stimulate a sufficiently strong and prolonged production of pro-inflammatory cytokines to cause a spondyloarthropathy is a study involving the stimulation of blood cells in culture with one component of the Gardasil vaccine, HPV-16. Tr. at 52-53 (citing M.A. Marks, et al., *Progesterone and 17ß-Estradiol Enhance Regulatory Response to Human Papillomavirus Type 16 Virus-Like Particles in Peripheral Blood Mononuclear Cells from Healthy Women*, CLINICAL & VACCINE IMMUN., 17(4): 609-17 (2010), filed as Pet. Ex. 87 ["Marks, Pet. Ex. 87"]). This study measured cytokine levels in blood cells taken from adult women after the cultured cells were stimulated with VLPs. Unsurprisingly, elevations in both pro- and anti-inflammatory cytokine levels, including TNF-α, were seen in the stimulated samples.

Doctor McCabe noted that a single *in vitro* immunization stimulated a variety of cytokines, including TNF-α, measured at 72 hours post immunization. Tr. at 55 (citing Marks, Pet. Ex. 87, at 612). He added that he would expect that the production of pro-inflammatory cytokines *in vivo* (within the body) would occur within the same time frame, specifying that he would expect TNF-α levels to be increased within three days. Tr. at 55-56. Finally, he stated that the level of TNF-α within three days of immunization "[c]ould be" high enough to cause AS in a genetically predisposed person. Tr. at 56.

However, the purpose of the cited study was not the measurement of cytokine levels in women before and after vaccination with Gardasil. As the stimulation by the VLPs occurred *in vitro*, it is unlikely that the cytokine response could reliably be related to the cytokine levels produced by a vaccine administered *in vivo*. Tr. at 180, 198. Moreover, as the study's purpose was to measure the effect of hormones on the immune response, it is unlikely that the researchers intended to draw any conclusions about immediate or delayed cytokine responses in vaccine recipients or that they were attempting to mirror *in vitro* the cytokine response *in vivo* to the vaccine.

[34] That is, showed antibodies to HPV.

Doctor McCabe acknowledged that "there is nothing that's really all that convincing that [Ms. Godfrey] had any inflammatory response or anything going on as a consequence of elevated, pro-inflammatory cytokines after her immunization[s]." Tr. at 74. Noting that there was no testing of Ms. Godfrey for markers of inflammation, he maintained that the best evidence that she had a high-level antibody response during the four weeks after the vaccination was the scientific evidence showing that over 90% of individuals seroconvert with such a response following the Gardasil vaccine. Tr. at 73-76 (discussing Frazer II, Pet. Ex. 71; Pinto I, Pet. Ex. 73; L. Pinto, et al., *Cellular Immune Responses to Human Papillomavirus (HPV)-16 L1 in Healthy Volunteers Immunized with Recombinant HPV-16 L1 Virus-Like Particles*, J. INFECT DIS., 188(2): 327-38 (2003), filed as Pet. Ex. 75 ["Pinto II, Pet. Ex. 75"]; T.G. Evans, et al., *A Phase 1 Study of a Recombinant Viruslike Particle Vaccine Against Human Papillomavirus Type 11 in Healthy Adult Volunteers,* J. INFECT. DIS., 183 (10): 1485-93 (2001), filed as Pet. Ex. 76 ["Evans, Pet. Ex. 76"]; Chao, Pet. Ex. 80.

Doctor McCabe testified that the antibody response after a single immunization "reaches a plateau between 12 and 18 days after immunization, and then declines." Tr. at 81-82 (citing I.H. Frazer, *Measuring serum antibody to human papillomavirus following infection or vaccination*, GYNECOLOGIC ONCOLOGY, 118:S8-11 (2010), filed as Pet. Ex. 70. However, I note that this citation refers to immunizations in general, and not specifically to HPV immunizations. *See id*. at S10. The paper cited also notes that no correlation between antibody level and protection against natural infection could be established because 40% of vaccinated individuals lacked measureable antibodies to HPV at 48 months after vaccination. *Id.* at S9.

When asked about evidence that Ms. Godfrey's cytokine levels remained elevated for four weeks after vaccination, he agreed that "no one measured antibody titer in Megan Godfrey, but you would expect that her antibody titers in response to HPV were increasing." Tr. at 39; *see also* Tr. at 74-75.

Doctor McCabe admitted that, despite his efforts to locate evidence to support a connection between vaccines in general and spondylopathy, he could not find any. Tr. at 59. Regarding Gardasil specifically, he stated that "epidemiological studies addressing the potential connection between Gardasil and ankylosing spondylitis, juvenile or otherwise, don't exist." Tr. at 40. He added that epidemiological studies addressing other autoinflammatory diseases have been performed, but "none . . . were appropriately powered to truly be able to tell us whether there was an increased risk or incidence of disease in those populations." Tr. at 40-41. Doctor McCabe was asked specifically about a safety study that involved 189,629 women who received at least one dose of the quadrivalent HPV vaccine. Tr. at 65 (referencing Chao, Pet. Ex. 80). He acknowledged that this study did not reveal an increased incidence of spondyloarthropathies like AS and JAS in the vaccinated population, but attributed the negative results to the rarity of the disease and the study lacking the power to detect a relationship of such a rare condition with the vaccine. Tr. at 41, 65-72.

E. Respondent's Evidence.

1. Summary of Dr. Rose's Report and Testimony.[35]

Doctor Rose's opinion rejecting a causal relationship between Gardasil and JAS rested on several points.[36] First, he noted that there are no epidemiologic studies linking such conditions to Gardasil. Res. Ex. A at 3. Second, he relied on Ms. Godfrey's strong genetic predisposition for developing JAS, as evidenced by "the presence of histocompatibility marker HLA-B27" as well as Crohn's disease in her father. *Id.* at 11. Moreover, she had not only a genetic predisposition but a known trigger for JAS in her medical history. Chronic micro-trauma, in the presence of HLA-B27, is a known trigger for JAS, and Ms. Godfrey was a high school athlete who was on her school's cheerleading team, which provided a basis for inferring the presence of micro-trauma. Tr. at 114-15, 162-64; Pet. Ex. 50. Doctor Rose opined that this combination, particularly in light of a first degree relative with Crohn's disease, fully accounts for her JAS. Tr. at 102-03. Finally, and perhaps most significantly, Dr. Rose explained why Dr. McCabe's assertions about the role of cytokines in JAS's etiology were incorrect. Cytokines do not cause JAS, although they play a role in the symptomology of the condition. Tr. at 116-18.

a. Epidemiology and Causation.

Doctor Rose testified that the epidemiologic evidence concerning the effects of Gardasil does not show any association with JAS or arthritic conditions in general. Tr. at 125-27. However, unlike Dr. McCabe, Dr. Rose found the Chao study, Pet. Ex. 80, to be sufficiently powered to detect a relationship between Gardasil and rheumatic disorders. Tr. at 123. He explained that the incidence of AS in the U.S. is about 7 cases per 100,000 persons, and that the male to female ratio is about 3-1 for adults and 7-1 for children. Tr. at 120-21, 146. Based on these ratios, and in the context of the nearly 190,000 women considered in the Chao study, Dr. Rose testified that "you should see about 1.5, 1.7 cases of ankylosing spondylitis in this [female] cohort." Tr. at 122. None were identified. Tr. at 121-24, 149-50. Although there were cases of juvenile

[35] Doctor Rose submitted his expert report in response to petitioner's report from Dr. Axelrod and prior to petitioner's filing of Dr. McCabe's report. *See* Res. Ex. A, filed Sept. 26, 2011. Although his report addresses some of the issues raised by Dr. McCabe, his testimony was in direct response to Dr. McCabe's opinions. Tr. at 133.

[36] I did not find Dr. Rose's reliance on the lack of any known association of natural HPV infection with spondyloarthropathy or any rheumatic disease (Tr. at 115-16; Res. Ex. A at 3, 5) to be a reason to reject Dr. McCabe's opinions. While it is true that natural HPV infections are not linked to chronic arthritic conditions like JAS, given Dr. McCabe's theory that an aberrant immune response rather than any specific action of the virus itself caused Ms. Godfrey's JAS, the lack of a link with natural infection is not significant. Doctor Rose agreed with Dr. McCabe that the natural infection and the vaccine are "very different stimuli." Tr. at 116. I thus do not discuss this argument in any more detail.

idiopathic arthritis,[37] the incidence in the study participants did not exceed the background rate expected in the population sampled. Tr. at 122-23, 150.

Aside from studies like Chao, there is other circumstantial evidence that a causal association between JAS and Gardasil is unlikely. There has been no change in the background rate of AS since Gardasil was introduced.[38] Tr. at 171 (Dr. Rose). Although more women are now diagnosed with JAS than there were in 1950-60, the increase is not temporally linked to the introduction of Gardasil. Doctor Rose attributed the increase in female diagnoses to greater awareness of the disease. Tr. at 171. He was unaware of any change in time of onset of either AS or JIA. *Id*. As Gardasil is recommended for administration to individuals in a narrow age range (between nine and 26 years of age (*see* Slade, Res. Ex. C-2, at 750)), a change in time of onset would be expected if the vaccine is causal.

b. Genetics and Triggers.

In explaining what is known about the causes of JAS, Dr. Rose testified that about 80-90% of AS cases have a genetic etiology and that the remaining cases are caused by environmental factors. Tr. at 109-11, 141 (citing Dougados, Pet. Ex. 54). Two identified environmental factors are bacterial infections, commonly of the intestinal tract, and trauma, specifically chronic micro-trauma associated with physical activity. Tr. at 113-15; *see also* Tr. at 138-39. Although there was no evidence that Ms. Godfrey suffered from enteritis, Dr. Rose pointed out that she was a cheerleader, and such activity would cause "continuous trauma to her Achilles tendon [and] sacroiliac joints." Tr. at 162-63.

According to Dr. Rose, about 20-40% of the cases of JAS or AS with a genetic etiology are linked to HLA-B27, with the remainder are associated with other genes. Tr. at 109-11. AS is considered a "polygenic disease," meaning that genes inherited in blocks or groups provide all the genetics needed to cause the condition. Tr. at 111-12; *see also* Ambarus, Pet. Ex. 79, at 2. He explained that the child of a person both carrying B27 and having AS who inherits her parent's variant of HLA-B27 is more likely to get AS than if the parent had B27, but no disease. Tr. at 112-13; *see also* Res. Ex. A at 11. This is so, not because parent and child were exposed to the same environmental factor such as a vaccine, but because the child "inherited the B27 plus

[37] Although JIA and AS are not the same disease, they present with similar symptoms. Tr. at 122-23 (Dr. Rose). About 80% of pediatric patients with spondyloarthropathy have a presentation that is indistinguishable from JIA. Tr. at 123; *see also* Tr. at 125-26 (Doctor Rose citing Appendix A to Chao, Pet. Ex. 80, filed as Res. Ex. C-24, and explaining that the Chao researchers did "everything possible to capture conditions like [Ms. Godfrey's]").

[38] Gardasil was licensed for use in the U.S. in 2006, and added to the Vaccine Injury Table later that same year. Slade, Res. Ex. C-2, at 750; Vaccine Injury Table, 42 C.F.R. § 100.3 (2011).

the other genes that produce causality."[39] Tr. at 112-13. He maintained that the onset of Ms. Godfrey's JAS following her Gardasil vaccination was "simply coincidental." Tr. at 102.

c. The Role of Cytokines in JAS.

Doctor Rose was most critical of the part of Dr. McCabe's theory that rested on the impact of the cytokine response in disease causation. He noted that the theory is "very unspecific" and one that he has not heard discussed in the general rheumatologic community. Tr. at 116-18. He did not dispute that the vaccine could cause a cytokine response, but did dispute that a cytokine response could cause the disease. Tr. at 116-17 (noting that almost any stress, including the common cold, sun exposure, and exercise can elicit a cytokine response). Acknowledging that a vaccine could elicit a cytokine response, he testified "[t]he fact that the HPV vaccine elicits a cytokine response doesn't make it more likely than any other life event . . . that can lead to excessive cytokines." Tr. at 117; *see also* Tr. at 158-59, 161-62.

He noted that HLA-B27 and other genes causally associated with AS "are not genes of hyper response to cytokines." Tr. at 117. As he explained, "B27 doesn't make her more prone to respond to or release more cytokines than the normal population upon a stimulation process." *Id*. This directly countered the portion of Dr. McCabe's theory that a cytokine response to Gardasil could trigger JAS in a "genetically susceptible" individual.

Doctor McCabe opined that pro-inflammatory cytokines such as TNF-α play a role in JAS, pointing to the use of TNF-α blockers as one of the primary treatments as support for their causal role. Tr. at 45-7. Doctor Rose agreed that medicines like Humira[40] that target TNF-α are one of the primary treatments for JAS. Tr. at 169. He also agreed that "interrupting TNF-alpha production results in less disease or less disease symptoms" in 70-80% of patients. *Id*. Most significantly, however, Dr. Rose disagreed that TNF-α, produced as the result of a vaccine or other life events, is a cause of JAS or similar conditions. Tr. at 170. TNF-α, rather than pushing a genetically predisposed person over the crest of the hill, produces disease symptoms such as pain and heat. However, TNF-α does not cause the disease itself. *Id.* TNF-α medications relieve pain, but do not affect the natural progression of the disease. *Id*. His assertions were supported by Dougados, Pet. Ex. 54, at 2131 (noting that the use of TNF blockers does not prevent ankylosing enthesitis) and 2133 (TNF blockers "halt joint destruction but fail[] to substantially slow new bone formation" in the disease process).

[39] On cross-examination, Dr. Rose agreed that "a very small fraction" of those who express HLA-B27, about 5-20%, develop AS. Tr. at 142-43. He noted, however, that people like Ms. Godfrey who have a parent with Crohn's disease, have a fourfold elevated risk. Tr. at 144.

[40] Humira, like Infliximab, the treatment Ms. Godfrey received, is a TNF-α inhibitor used to treat inflammation in a variety of medical conditions, including AS.

d. Timing.

Doctor Rose agreed with Dr. McCabe that measuring antibody titers to HPV is a method to determine if the vaccine is effective. However, he disagreed that relating "antibody formation to the onset of the disease" proves anything about causation, because onset of symptoms such as Ms. Godfrey displayed does not tell us when her disease began. Tr. at 129; *see also* Tr. at 165 (stressing the difference between onset of symptoms and onset of disease). Based on when her symptoms first occurred, Dr. Rose could not opine when Ms. Godfrey's disease process actually started. Tr. at 129. Thus, the evidence regarding timing between vaccination and symptom onset in Ms. Godfrey could not be reliable evidence of causation as Dr. McCabe asserted, because symptom onset did not mark the onset of the disease process. For example, Ms. Godfrey had inflammation in both sacroiliac joints but only had pain in one of them, at least initially, demonstrating the separation between symptom onset and disease process. Tr. at 129; Pet. Exs. 8, p. 14; 9, p. 122.

2. Summary of Dr. Zweiman's Report and Testimony.

Doctor Zweiman also set forth several reasons that contradict Dr. McCabe's causation theory. First, like Dr. Rose, he found the lack of support in the medical literature for a causal association between HPV immunization and JAS[41] to be a significant reason for rejecting the theory. Res. Ex. C at 3. He also rejected Dr. McCabe's assertions regarding the role of cytokines in the disease process, noting that under Dr. McCabe's theory, in order to cause JAS, cytokine production would have to occur in a "prolonged, consistent fashion." Tr. at 200. Third, he opined that her risk factors fully accounted for her AS. Res. Ex. C at 3.

a. Epidemiology and Medical Literature.

Doctor Zweiman cited to numerous pre- and post-licensure studies involving HPV vaccines and absence of reports of persistent joint symptoms exceeding the background rate expected.[42] Thus, this is not a case where epidemiologic evidence is lacking. The epidemiology exists, and is not supportive of the theory.

[41] Throughout his expert report, Dr. Zweiman used the broad term, "spondyloarthropathy" ["Sp"] to refer to a group of "several related but distinct disorders," including AS. Res. Ex. C at 2.

[42] Res. Ex. C at 3 (citing Slade, Res. Ex. C-2 at 750, 755-56 (examining VAERS reports in the 2.5 years after licensure and finding only 13 reports of rheumatoid arthritis which did not exceed the background rate expected, but noting that VAERS reports should be viewed with caution); CDC, Res. Ex. C-6; *Quadrivalent Human Papillomavirus Vaccine ,Report of the Advisory Committee on Immunization Practices (ACIP)*, MMWR 56(RR02): 1-24 (2007), filed as Res. Ex. C-4 (reporting no statistically significant differences between placebo and vaccine recipients for various arthritic diagnoses); B. Lu, et al., *Efficacy and Safety of Prophylactic Vaccines against Cervical HPV Infection and Diseases among Women: A Systematic Review & Meta-Analysis*, BMC INFECT. DIS. 11: 13 (2011), excerpts filed as Res. Ex. C-3 at 4 (reporting no statistically significant difference in the risk for serious adverse events between vaccine and control groups).

Addressing the Chao article, Dr. Zweiman reasoned that if 6-8% of the Americans are HLA-B27 positive, and 35 million doses of Gardasil have been administered in the U.S., one would expect that the incidence of JAS among the over one million HLA-B27 positive individuals who received the vaccine would be notable if the HPV vaccine was a trigger. Tr. at 182. In other words, if JAS could be triggered by the HPV vaccine, it would not be such a rare condition, given the number of doses administered since Gardasil was introduced.[43] Tr. at 182-83. Asked what sort of evidence he would look for if there were a causal relationship between the HPV vaccine and AS, Dr. Zweiman stated that he would expect "safety signals . . . raised by sizeable numbers of reports through the [Vaccine Adverse Events Reporting System]," as well as "some evidence of real biologic plausibility." Tr. at 183-84; *see also* Tr. at 187. He stated that he has seen no such evidence. Tr. at 184, 187.

b. Cytokines and Immune Response.

Before explaining what he found deficient in Dr. McCabe's cytokine theory, Dr. Zweiman offered some background as to "what happens when an individual is immunized with a potent immunogen." Tr. at 176. He stated that "there is an initial activation, a so-called primary immune response, and that when that individual is then re-exposed to the antigen . . . one would expect it likely that there would be an exaggerated proliferative response." Tr. at 176 (citing Pinto I, Pet. Ex. 73). He added that, in addition to a proliferative response, there would be a stimulation of cytokine production, including pro-inflammatory cytokines like TNF- α, and that "it would not be surprising that one would get a more prominent lymphocyte proliferation as well." Tr. at 177. He explained that pro-inflammatory cytokine elaboration is a common response to infection and even trauma. Tr. at 179. Concerning the HPV vaccine specifically, he agreed that HPV VLPs are effective at inducing pro-inflammatory cytokines. Tr. at 212.

Doctor Zweiman testified that the innate immune response differs from the adaptive immune response in two ways. The first difference is the "major cellular players in a production of [the] immune response," and the second is that the innate immune response does not have "immunologic memory such as one finds in adaptive responses." Tr. at 179. Concerning the second point, he stated that, "to get a repeat or continued elaboration of the products of inflammatory cytokine, you have to have continued stimulation by the initial stimulus." Tr. at 179-80. Doctor Zweiman explained that in sustained cytokine production, an innate immune response "does not carry immunologic memory like the adaptive immune response, so that for the most part one

[43] In opining that Ms. Godfrey was "genetically susceptible" to developing JAS, and that her response to the vaccine pushed her into its development (Tr. at 56), Dr. McCabe appeared to be referring to the HLA-B27 marker. Thus, Dr. Zweiman's point that others with the same marker would be pushed into JAS development by the same process is well-taken. It is possible that Dr. McCabe was opining that there was something very unique about Ms. Godfrey, but if so, he never identified any "x factor" that separated her from the more than 1,000,000 other young women with HLA-B27 who also received HPV vaccines.

needs to have a continued stimulation of more production by cells," of which there is no evidence in studies. Tr. at 202-03.

Thus Dr. Zweiman opined that Dr. McCabe's theory, as described using a hill analogy, is flawed. Tr. at 180, 199. He maintained that the notion of a vaccine-elicited pro-inflammatory cytokine response that pushes an individual over the top of the hill and leads to disease development on its own, "goes against what is generally known about the production of [pro-]inflammatory cytokines." Tr. at 180. He opined that there must be continued pro-inflammatory cytokine production in order to continue a disease process under this theory and that Dr. McCabe presented no convincing evidence of continued stimulation. Tr. at 180, 198-99, 203. Doctor Zweiman based this opinion on "the fact that in individuals who have high even blood levels of some of these pro-inflammatory cytokines associated with certain diseases, when the levels go down, the clinical adverse manifestations decrease or go away completely." Tr. at 203-04.

Building on Dr. Rose's testimony about the role of cytokines in JAS, Dr. Zweiman explained why the studies done by the Pinto group, *E.g.*, Pinto I, Pet. Ex., were not supportive of Dr. McCabe's causation theory. As Dr. Rose testified, a transient increase in the production of pro-inflammatory cytokines such as TNF-α would not cause sustained symptoms or disease. Doctor Zweiman explained, relying on the Pinto I study as well as basic immunological principles, that Gardasil did not produce any sustained increase in cytokine levels in vaccinated individuals. Tr. at 178-79. Cultured blood cells drawn from individuals who had received HPV vaccines produced higher levels of cytokines than individuals who had not received the vaccines, but only when the cultured blood cells were again exposed to HPV vaccines *in vitro*. Pinto I, Pet. Ex. 73, at 3558-61.

In his expert report, Dr. McCabe relied on Pinto I, Pet. Ex. 73, citing it for the statement that individuals immunized with HPV L1 VLPs, the immunogenic component of Gardasil, produce "high levels of both adaptive and innate immune cytokines." Pet. Ex. 52 at 4. The difficulty is that the this study[44] and several others from the same

[44] The Pinto I study was not terribly complex, but the explanation in the text is sometimes unclear. Researchers measured 11 cytokines, including TNF-α, before and after vaccination in twenty-four women, four of whom belonged to the control group and received placebo injections. At "month zero," prior to the initial injection, the researchers drew blood samples. The vaccinated group then received a dose of the HPV-16 L1 VLP vaccine and the control group received a placebo. Second injections were administered one month later. At month two, a second set of blood samples was taken. Final injections were administered at six months, and the final blood samples were taken a month later, seven months after the initial blood draw. Pet. Ex. 73 at 3556-57.

The blood samples from both the vaccinated and control groups were divided into samples for *in vitro* stimulation. *Id.* at 3557, 3562. *S*amples from each group, for each interval, were either not stimulated, or stimulated with one of the following: (1)10 µg of the VLP present in the vaccine; (2) 1.0 µg of the VLP; or (3) a control substance that would not stimulate a reaction (unstimulated samples). The researchers then measured cytokine levels in the samples. *Id.* at 3558 (Table 1). For both the vaccinated and control groups, cytokine levels in the unstimulated samples were relatively similar at months zero, two, and seven. *Id.* at 3560.

Johns Hopkins group of researchers found increased cytokine levels only when those who were already vaccinated with HPV L1 VLPs had blood stimulated with more HPV L1-VLPs. *See, e.g.*, Pinto I, Pet. Ex. 73 at 3556-59. This study was not designed to measure cytokine levels produced by the vaccine itself, but rather whether increased cytokine levels could be used as a surrogate for antibody response. *Id.* at 3556-57. Although the study shows that women who were vaccinated against HPV mounted a robust cytokine response in the presence of HPV VLPs, it did not show a significant increase in cytokine levels in the absence of such a challenge. *Id.* at 3558 (Table 1).

c. Genetics and Predisposition.

According to Dr. Zweiman, "Ms. Godfrey was in an age range in which [JAS] occurs spontaneously." Res. Ex. C at 3. Based on her expression of HLA-B27 and its prevalence in people with JAS, Dr. Zweiman, like Dr. Rose, opined that her JAS developed "by chance." *Id.* at 3; Res. Ex. A at 11.

V. Analysis of Causation Evidence

A. Applying *Althen.*

The Federal Circuit has set forth three factors petitioners must establish to prove causation in off-Table cases. *See Althen*, 418 F.3d at 1278. *Althen* requires petitioners to provide: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* All three prongs of the *Althen* test must be satisfied by preponderant evidence. *de Bazan,* 539 F.3d at 1351-52; *Caves*, 100 Fed. Cl. at 132 (finding that "[w]hen a petitioner seeks to demonstrate causation in fact by meeting the three *Althen* requirements, each of those requirements must be proven by a preponderance of the evidence"), ***aff'd per curiam***, 463 Fed. Appx. 932, 2012 WL 858402 (Fed. Cir. 2012). Therefore, petitioner must establish a medical theory causally connecting the vaccination and the injury by preponderant evidence. *Althen*, 418 F.3d at 1278.

1. Lack of Reliable General Causation Evidence.

Petitioner's causation case is based on the HPV vaccination she received on August 22, 2007, "substantially contributing" to her development of JAS. The medical theory propounded—that the pro-inflammatory cytokine proliferation caused by a single Gardasil vaccine can push a genetically susceptible individual to develop JAS—fails the reliability test. The major difficulty with Dr. McCabe's theory is that there is no evidence that pro-inflammatory cytokines play any role in the pathogenesis of JAS, although they

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The mean blood cytokine levels from both placebo and vaccine recipients were remarkably similar in the samples not challenged by stimulation with HPV VLP. Cytokine levels were significantly different when the HPV VLPs were used to stimulate the blood from the vaccine recipients. *Id.* at 3558 (Table 1).

do play a role in the symptoms displayed. Doctor Rose's testimony, that pro-inflammatory cytokines cause symptoms of JAS but not the disease itself, is unrebutted. The Dougados article, filed by both parties, (Pet. Ex. 54 and Res. Ex. C-1 at 2132-33) supports Dr. Rose's testimony. Treatment with TNF-α inhibitors alleviates symptoms, but does not affect the progression of the disease. *Id.*

Although less devastating for petitioner's case, there are other problems with Dr. McCabe's theory. There is no evidence that a genetic susceptibility to develop JAS also encompasses a genetic susceptibility to increases in pro-inflammatory cytokines. Although Dr. McCabe argued that the strong genetic component to petitioner's disease somehow left her vulnerable to the cytokine response to the vaccine, he had no answer for Dr. Rose's testimony that the genetics of AS, specifically HLA-B27, "are not genes of hyper response to cytokines" (Tr. at 117).

Gardasil produces only a transient increase in cytokine levels, and there is no evidence that a transient increase can cause symptoms of JAS, much less the disease itself. Moreover, there is no evidence that the cytokine proliferation caused by Gardasil is of the same nature or intensity as the bacterially-based gastrointestinal infections that have been temporally associated with triggering onset of JAS. Ms. Godfrey's genetic background, coupled with a family history and the presence of a known "trigger" for development of JAS, fully account for her diagnosis. Finally, Gardasil was extensively studied, pre- and post-licensure, for evidence of adverse events. No study has found any association between the full, three-injection regimen, much less the one vaccination Ms. Godfrey received, and arthritic conditions or JAS.

In essence, Dr. McCabe took evidence that Gardasil, like many life events, including exercise, sunlight, and infections, transiently increases proliferation of pro-inflammatory cytokines, and made this increase into a trigger for an event (the development of JAS) that did not require one.[45] The biological mechanism posited is not a reliable theory because there is no evidence that cytokines cause the disease.

This problem illustrates the difficulty of relying on a theory propounded by a scientist who does not research, diagnose, or treat JAS. Doctor McCabe understood and conveyed that JAS is recognized as an autoinflammatory disorder, that pro-inflammatory cytokines such as TNF-α have been found in the synovial fluid of JAS patients, and that the HPV vaccine provokes cytokine production, including pro-inflammatory cytokines, in recipients. What he apparently failed to understand is that pro-inflammatory cytokines play a role in JAS's symptomology, but there is no evidence that they play a role in its pathogenesis or in the bone remodeling that is the hallmark of the disease.

[45] Doctor McCabe testified that "infection, stress, and trauma are all triggers associated with the onset of JAS" (Tr. at 85), tacitly acknowledging that vaccination was not considered a known risk factor.

Moreover, Ms. Godfrey exhibited substantial risk factors for developing JAS, as she carries a disease-causing version of HLA-B27, which she inherited from a first degree relative who also carries HLA-B27 and has Crohn's disease. According to Dr. Rose, this gave her a one-in-five chance of developing JAS; a condition found in about seven of every 100,000 individuals. She also had a known trigger in her history; she was a high school cheerleader, making her susceptible to chronic micro-trauma in hips and ankles. Although there was some discussion about the fact that most people with HLA-B27 do not develop JAS or similar diseases, the very high percentage of those who develop JAS as children (one study indicated that in children with JAS, 97% carry the HLA-B27 marker),[46] coupled with Ms. Godfrey's inherited HLA-B27 marker and a first degree relative with Crohn's disease, are all strong indications of her high genetic predisposition to developing JAS.

Although Dr. McCabe holds an academic appointment at a medical school, he is not a physician. He has considerable expertise in immunotoxicology, and I have previously relied upon his expert opinion on mercury and its effects on the immune system and the brain.[47] However, in this case he is out of his depth in presenting a theory on the cause of a medical condition, with little, if any, support in the medical and scientific literature. The fact that he derives nearly all of his income at present from preparing and presenting expert opinions is also a factor in assessing the reliability of those opinions.

In contrast, respondent's expert, Dr. Rose, diagnoses and treats such conditions, and is familiar with the etiologic factors that are accepted as causal in the scientific and medical communities. Given Dr. Rose's background and experience, I accord his opinion on causality more weight than I give to Dr. McCabe in this case. Moreover, Dr. Zweiman persuasively explained why Dr. McCabe's theory that a vaccine-induced cytokine response pushed a genetically predisposed person over the edge into an auto-inflammatory condition was very unlikely.

Simply put, respondent's experts proffered opinions that I find more reliable and persuasive than those of Dr. McCabe. Genetics alone is a sufficient and "but for" cause for Ms. Godfrey's condition.

2. A Logical Connection and Timing.

Given my conclusions regarding *Althen's* first prong, it is unnecessary to address prongs two and three. I briefly note that there is nothing in Ms. Godfrey's medical history linking her JAS to her Gardasil vaccination, aside from one note indicating that she had been vaccinated a month before symptoms began. As the Federal Circuit has indicated, a temporal relationship alone is insufficient to demonstrate a logical

[46] Lin, Pet. Ex. 56, at 577.

[47] *Snyder v. Sec'y, HHS*, No. 01-162V, 2009 WL 332044, at *18 (Fed. Cl. Spec. Mstr. Feb. 12, 2009).

connection between these two events. *Grant v. Sec'y*, HHS, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A reference in a medical record to a vaccination being an antecedent event is insufficient to attribute to a treating physician any opinion that the vaccine was somehow responsible. *See Moberly*, 592 F.3d at 1323; *Caves*, 100 Fed. Cl. at 141-42.

The last *Althen* factor burdens the petitioner with establishing, by preponderant evidence, a proximate temporal relationship between vaccination and injury. *Althen*, 418 F.3d at 1278. Analogizing to the time frame when an immunological response to a vaccine would be expected to occur, producing the cytokines central to his theory, Dr. McCabe contended that a month between vaccination and onset of symptoms was scientifically appropriate. Doctor Rose explained the fallacy in this approach. Symptoms do not equate to onset of disease in JAS. He testified that it would be impossible to determine when the onset of her disease actually began. In support, he noted that Ms. Godfrey initially only complained of left hip pain, but imaging studies showed evidence of disease in both hips. I accept Dr. Rose's testimony, given his expertise in treating AS.

VI. Conclusion

Petitioner has failed to establish any of the *Althen* prongs by preponderant and reliable evidence. She has failed to demonstrate that Gardasil can cause JAS or that it did so in her case. The petition for compensation is therefore DENIED. The clerk is directed to enter judgment accordingly.

IT IS SO ORDERED.

s/Denise K. Vowell
Denise K. Vowell
Chief Special Master